(19) Europäisches Patentamt
European Patent Office
Office européen des br vets

(11) Publication number: **0 154 528**
A3

(12) # EUROPEAN PATENT APPLICATION

(21) Application number: **85301414.0**

(22) Date of filing: **01.03.85**

(51) Int. Cl.⁴: **C 07 C 49/248**
C 07 C 33/48, C 07 C 121/60
C 07 C 121/75, C 07 C 147/0-2
C 07 D 521/00, A 61 K 31/33
A 61 K 31/10, A 61 K 31/12
A 61 K 31/275

(30) Priority: **07.03.84 GB 8406000**

(43) Date of publication of application:
11.09.85 Bulletin 85/37

(88) Date of deferred publication of search report: **04.01.89**

(84) Designated Contracting States:
AT BE CH DE FR GB IT LI LU NL SE

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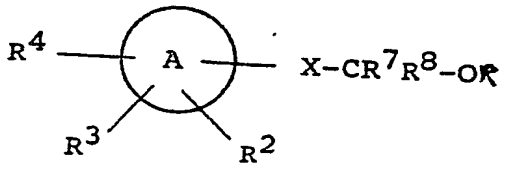
(54) **Alkene, alkyne or cycloalkylene derivatives.**

(57) A compound of the formula

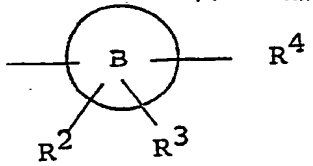


halogenoalkyl; and wherein R^8 is carbamoy., alkyl, cycloalkyl, alkenyl, alkynyl, halogenoalkyl, halogenoalkenyl, halogenoalkynyl, alkanoyl, alkylcarbamoyl, dialkylcarbamoyl or aroyl; or wherein R^8 is alkyl or alkenyl which bears one or more substituents selected from cyano, carbamoyl, amino, hydroxy, alkanoyl, alkoxy, alkylthio, alkenylthio, alkylsulphinyl, alkenylsulphinyl alkylsulphonyl, alkenylsulphonyl, alkanoylamino, alkoxycarbonylamino, alkylsulphonamido, alkylamino, dialkylamino, dialkylsulphamoyl, aroyl, aryl, arylthio, arylsulphinyl, arylsulphonyl, heterocyclylthio, heterocyclylsulphinyl and heterocyclylsulphonyl; or wherein R^8 has the formula

wherein X has the formula CH_2

$-CR^5=CR^6-$ $-C\equiv C-$ or $-CR^5-CR^6$

wherein ring A is phenyl, naphthyl or heterocyclic;
wherein R^1 is hydrogen, alkyl, alkanoyl or aroyl;
wherein R^2, R^3 and R^4, which may be the same or different, each is an electron withdrawing substituent selected from halogeno, nitro, cyano, trifluoromethyl, alkylthio, alkylsulphinyl and alkylsulphonyl or each is hydrogen, alkyl, alkoxy or dialkylamino provided that when ring A is phenyl or naphthyl at least one of R^2, R^3 and R^4 is an electron-withdrawing substituent; wherein R^5 and R^6, which may be the same or different, each is hydrogen, halogeno or alkyl; wherein R^7 is alkyl or



wherein ring B is phenyl, naphthyl or heterocyclyl and wherein R^2, R^3 and R^4 have any of the meanings stated above, provided that when R^7 is methyl R^8 is not also methyl.

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European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequ nt proceedings, as the European search report

Application number

EP 85 30 1414

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
X	FR-A-2 314 912 (L. GIVAUDAN & CIE.)		C 07 C 49/248
	* Claim 15 *	1,2	C 07 C 33/48
	--		C 07 C 121/60
X	US-A-4 139 561 (ONOPCHENKO et al.)		C 07 C 121/75
	* Column 7, formula *	1,2	C 07 C 147/02
	--		C 07 D 521/00
E	EP-A-0 193 303 (I.C.I.)		A 61 K 31/33
	* Claims *	1-3,6-10	A 61 K 31/10
			A 61 K 31/12
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TECHNICAL FIELDS SEARCHED (Int. Cl.4)

C 07 C
C 07 D

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.

Claims searched completely: 4,5

Claims searched incompletely: 1-3,6-10

Claims not searched:

Reason for the limitation of the search: The use of the undefined wording "heterocyclic" makes a complete search for this type of compounds impossible; hence, when "heterocyclic" is used, the search was limited to the explicitely mentioned compounds. Besides this, the use of dependent meanings of substituents and the repeated -and even abusive- use of "or" makes it difficult to evaluate which groups of compounds are really claimed. This application hardly meets the requirements of arts. 82 and 84 of the European Patent Convention.

Place of search	Date of completion of the search	Examiner
The Hague	10-10-1988	VAN GEYT

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : int rmediate document

T : theory or principle underlying the invention
E : arlier patent document, but publish d on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO Form 1505.1 03.82

(19) Europäisches Patentamt
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Office europé n des brevets

(11) Publication number: **0 311 447 A1**

(12) # EUROPEAN PATENT APPLICATION

(21) Application number: 88309413.8

(22) Date of filing: 07.10.88

(51) Int. Cl.4: C 07 D 233/64
C 07 D 233/58, A 61 K 31/415

(30) Priority: 09.10.87 GB 8723715

(43) Date of publication of application:
12.04.89 Bulletin 89/15

(84) Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

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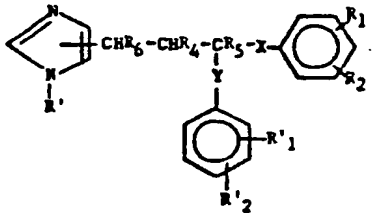
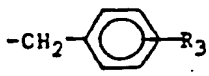
(54) **Aromatase inhibiting 4(5)-imidazoles.**

(57) Imidazole derivatives of the formula:



wherein R_1, R_2, R'_1, and R'_2 which can be the same or different, are H, CH_3, C_2H_5, OCH_3, OH, CH_2OH, NH_2 or halogen; R' is H or



where R_3 is H, CH_3, or halogen; R_4 is H and R_5 is H or OH and R_6 is H or OH or one of R_5 and R_6 is H and the other, together with R_4, forms a bond and X and Y, which can be the same or different, are a bond, a straight C_{1-2}-alkyl or the corresponding alkenyl, and pharmaceutically acceptable salts thereof exhibit valuable pharmacological properties, especially aromatase inhibiting effects and are useful in the treatment of estrogen dependent diseases, e.g. breast cancer. Antimycotic and antifungal properties have also been found.

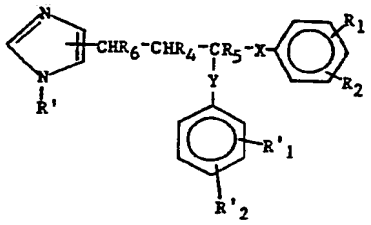
EP 0 311 447 A1

Description

AROMATASE INHIBITING 4(5)-IMIDAZOLES

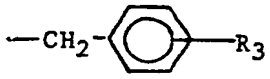
The present invention relates to substituted imidazole derivatives and their non-toxic, pharmaceutically acceptable acid addition salts, and their preparation, to pharmaceutical compositions containing the same and to their use.

The imidazole derivatives of the present invention have the general formula:



(I)

wherein R_1, R_2, R'_1 and R'_2, which can be the same or different, are H, CH_3, C_2H_5, OCH_3, OH, CH_2OH, NH_2 or halogen; R' is H or



where R_3 is H, CH_3 or halogen; R_4 is H and R_5 is H or OH and R_6 is H or OH or one of R_5 and R_6 is H and the other forms, together with R_4, a bond, and X and Y, which can be the same or different, are a bond, a straight C_{1-2}-alkyl or the corresponding alkenyl.

The non-toxic pharmaceutically acceptable acid addition salts of these compounds are also within the scope of the invention.

The compounds of the formula (I) form acid addition salts with both organic and inorganic acids. They can thus form many pharmaceutically usable acid addition salts, as, for instance, chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, formates, tartrates, maleates, citrates, benzoates, salicylates, ascorbates and the like.

The invention includes within its scope pharmaceutical compositions comprising at least some of the compounds of formula (I) or a non-toxic, pharmaceutically acceptable salt thereof, and a compatible pharmaceutically acceptable carrier therefor.

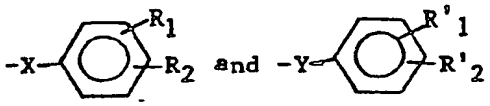
The invention provides, for example, the following specific compounds of formula (I):

4-(3,3-diphenyl-3-hydroxypropyl)-1H-imidazole
4-[3,3-bis(4-chlorophenyl)-3-hydroxypropyl]-1H-imidazole
4-[3,3-bis(2-methylphenyl)-3-hydroxypropyl]-1H-imidazole
4-[3,3-bis(3-methylphenyl)-3-hydroxypropyl]-1H-imidazole
4-(3,3-diphenylpropen-2-yl)-1H-imidazole
4-[3,3-bis(4-chlorophenyl)propen-2-yl]-1H-imidazole
4-[3,3-bis(2-methylphenyl)propen-2-yl]-1H-imidazole
4-[3,3-bis(3-methylphenyl)propen-2-yl]-1H-imidazole
4-(3,3-diphenylpropyl)-1H-imidazole
4-[3,3-bis(2-methylphenyl)propyl]-1H-imidazole
1-benzyl-5-[3,3-bis(4-chlorophenyl)-3-hydroxypropyl]-1H-imidazole
1-benzyl-5-[5-(2,6-dimethylphenyl)-3-hydroxy-3-(2,6-dimethylphenylethyl)pentyl]-1H-imidazole
1-benzyl-5-[3,3-bis(4-chlorophenyl)propen-2-yl]-1H-imidazole
4-[3-(4-chlorophenyl)-3-hydroxy-3-phenylpropyl]-1H-imidazole
1-benzyl-4-(3,3-diphenylpropyl)-1H-imidazole
1-benzyl-5-(3,3-diphenylpropyl)-1H-imidazole
4-[5-(2,6-dimethylphenyl)-3-(2,6-dimethylphenylethyl)pentyl]-1H-imidazole
4-[3,3-bis(3-methylphenyl)propyl]-1H-imidazole
1-(4-chlorobenzyl)-4-(3,3-diphenylpropyl)-1H-imidazole
1-(4-chlorobenzyl)-5-(3,3-diphenylpropyl)-1H-imidazole
4-[5-(2,6-dimethylphenyl)-3-hydroxy-3-(2,6-dimethylphenylethyl)pentyl]-1H-imidazol
4-[3,3-bis(3-fluorophenyl)propen-2-yl]-1H-imidazole

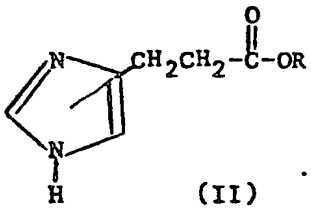
4-[3,3-bis(3-fluorophenyl)propyl]-1H-imidazole
4-[3,3-bis(3,5-dimethylphenyl)propyl]-1H-imidazol
1-benzyl-5-(3,3-diphenylpropen-2-yl)-1H-imidazole
1-benzyl-5-[3,3-bis(3,5-dimethylphenyl)-3-hydroxypropyl]-1H-imidazole
1-benzyl-5-[3,3-bis(3,5-dimethylphenyl)propen-2-yl]-1H-imidazole
1-benzyl-5-[3,3-bis(2-methoxyphenyl)propen-2-yl]-1H-imidazole
1-benzyl-5-[3,3-bis(3-methoxyphenyl)propen-2-yl]-1H-imidazole
1-benzyl-5-[3,3-bis(4-methoxyphenyl)propen-2-yl]-1H-imidazole
1-benzyl-5-[3,3-bis(2,3-dimethylphenyl)propen-2-yl]-1H-imidazole
1-benzyl-5-[3,3-bis(2-methylphenyl)propen-2-yl]-1H-imidazole
1-benzyl-5-[3,3-bis(3-methylphenyl)propen-2-yl]-1H-imidazole
1-benzyl-5-[3,3-bis(4-methylphenyl)propen-2-yl]-1H-imidazole
1-benzyl-5-[3,3-bis(3,5-dimethylphenyl)propyl]-1H-imidazole
1-benzyl-5-[3,3-bis(3-methoxyphenyl)propyl]-1H-imidazole
4-[3,3-bis(3,5-dimethylphenyl)propyl]-1H-imidazole
4-[3,3-bis(2,3-dimethylphenyl)propyl]-1H-imidazole
4-[3,3-bis(2-methoxyphenyl)propyl]-1H-imidazole
4-[3,3-bis(3-methoxyphenyl)propyl]-1H-imidazole
4-[3,3-bis(4-methoxyphenyl)propyl]-1H-imidazole
4-[3,3-bis(4-methylphenyl)propyl]-1H-imidazole

The compounds of the present invention have been found to possess aromatase inhibiting properties and are therefore valuable i the treatment of estrogen dependent diseases, e.g. breast cancer. Antimycotic and antifungal properties have also been found.

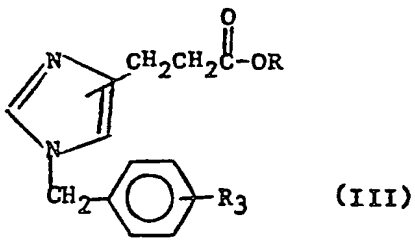
According to a feature of the invention, the compounds of formula I wherein the branches



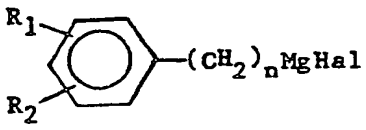
are identical are prepared by a successive sequence of reactions comprising a Grignard reaction of 4(5)-imidazole propionic acid alkyl ester (II) or its 1-benzyl derivative III with an appropriate aryl- or arylalkylmagnesium halide IV following the loss of water and hydrogenation



(II)

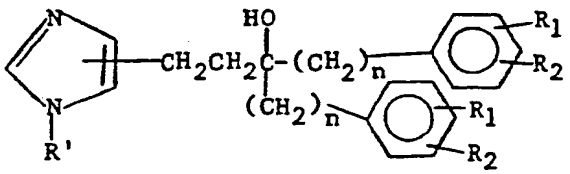


(III)



(IV)

In the formulae (II) to (IV) R is alkyl, R_3 is H, CH_3 or halogen, n is 0 to 2 and R_1 and R_2, which can be the same or different, are H, CH_3, C_2H_5, OCH_3, OH, CH_2OH, NH_2 or Hal (Hal = halogen). The first reaction step, the Grignard-reaction, leads to the following compounds of formula (I):



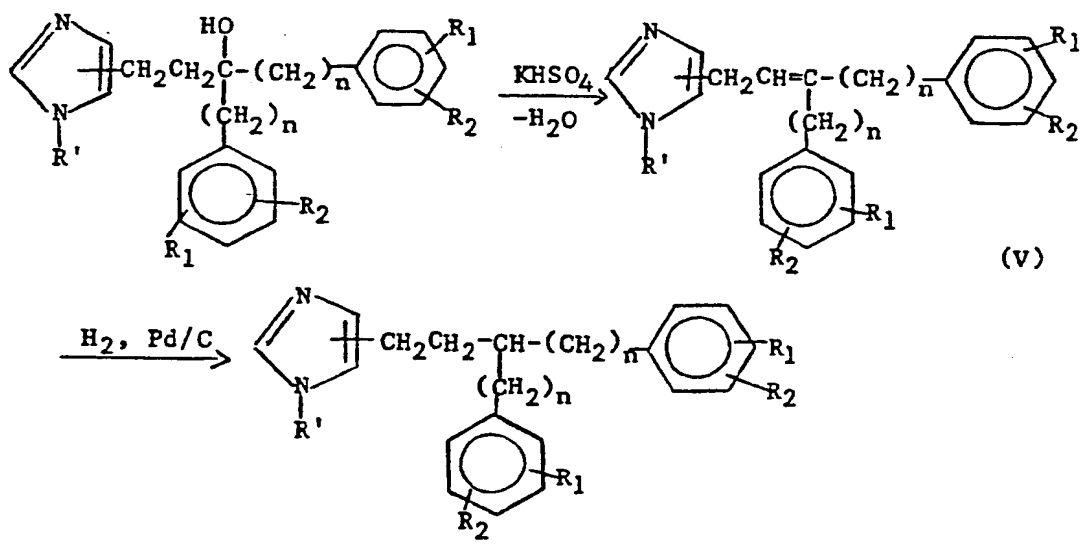
In this reaction the arylalkylmagnesium halide derivative can be, for example, an arylalkylmagnesiumbromide derivative, which is prepared by reacting the corresonding arylalkylbromide derivative with magnesium. Suitable solvents for the reaction include a variety of ethers, preferably tetrahydrofuran.

The arylalkylmagnesiumhalide derivative is prepared in the usual way be adding the arylalkylhalide derivative in a suitable solvent, e.g. tetrahydrofuran, dropwise onto magnesium turnings covered by tetrahydrofuran, at the boiling point of the reaction mixture. When the magnesium turnings have reacted, the mixture is cooled slightly and the 4(5)-imidazole propionic acid alkyl ester or its 1-benzylsubstituted derivative is added in solid form in small portions or dropwise in tetrahydrofuran.

After the addition, the reaction mixture is refluxed until all of the 4(5)-imidazole derivative has reacted. The reaction time varies between one and five hours.

Further according to the feature of the invention, the compounds of formula (I), wherein R_4 and R_5 both are hydrogen or together form a bond, are prepared by dehydration of the compounds of formula (I), where R_5 is OH, and by catalytic addition of hydrogen in the second step. Water is eliminated by usual methods, i.e. by heating with concentrated hydrochloric acid or by heating with dry potassium hydrogen sulfate. The unsaturated derivatives (V) (the compounds of formula (I) wherein R_4 and R_5 together form a bond) are isolated and after that hydrogenated. Alternatively they can be hydrogenated directly in an acid medium without previous isolation. The hydrogenation is conveniently carried out at room temperature with good stirring in alcohol, e.g. ethanol in the presence of a catalyst in a hydrogen atmosphere. Suitable catalysts are for example platinium oxide, palladium-on-carbon or Raney-nickel.

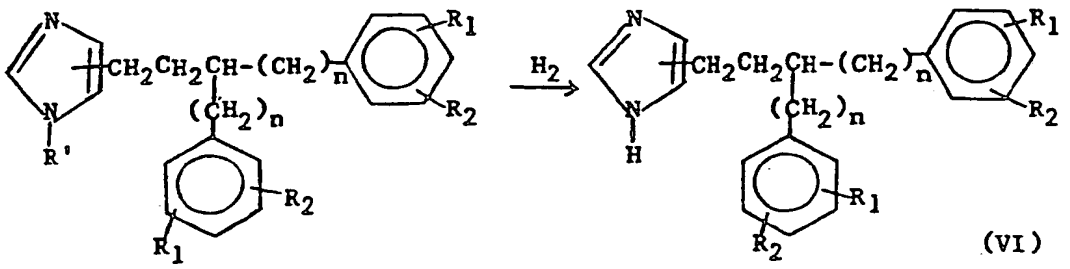
The reaction scheme for these steps can be illustrated as follows:



(V)

If R' is a substituted or unsubstituted benzyl, this group may be removed by hydrogenation as well. In this case the hydrogenation is performed in an acidic medium such as hydrochloric acid-ethanol mixture at elevated temperature.

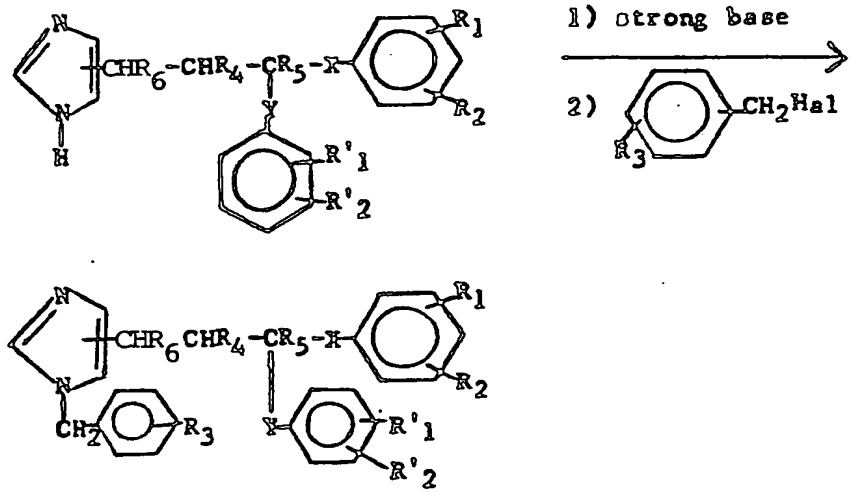
The reaction scheme of this hydrogenation which I ads to compounds of formula (I) wherein R_4 and R_5 both are hydrogen can be illustrated as follows:



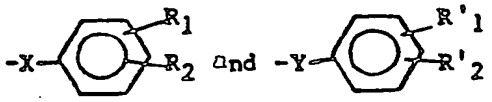
(VI)

The compound (VI) can also be prepared directly from the compounds (V) by hydrogenating both the double bond and the protecting benzyl group at the same time.

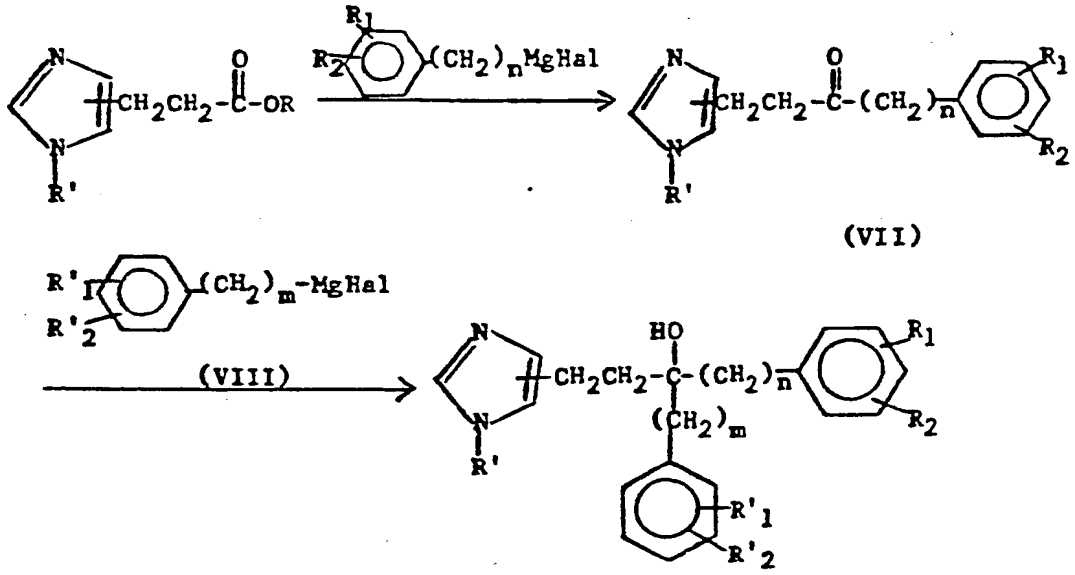
Another method for the preparation of compounds of formula (I) where R' is a benzyl is the benzylation of the corresponding compound where R' is hydrogen. The starting compound is first treated with a strong base such as sodium hydroxide in water or sodium hydride in an appropriate solvent, e.g. dimethyl formamide to give the alkali metal salt of the imidazole and then in the second step adding to this benzyl halide. The reaction scheme can be illustrated as follows:



Yet another process for the preparations of compounds of formula (I) wherein the branches



are different, comprises in the first stage a series of two successive Grignard reactions starting from 4(5)-imidazole propionic acid alkyl ester or from 1-benzyl-4(5)-imidazole propionic acid alkyl ester as previously. Now, however, the amount of the Grignard reagent is reduced as well as the reaction temperature, to stop the reaction at the ketone stage to give the 4(5)-imidazolylpropyl aryl or arylalkyl ketone (VII), which further is reacted with another Grignard reagent (VIII) to give a compound of the formula (I) where R_5 is OH. The reactions are illustrated as follows:

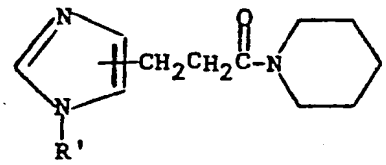


(VII)

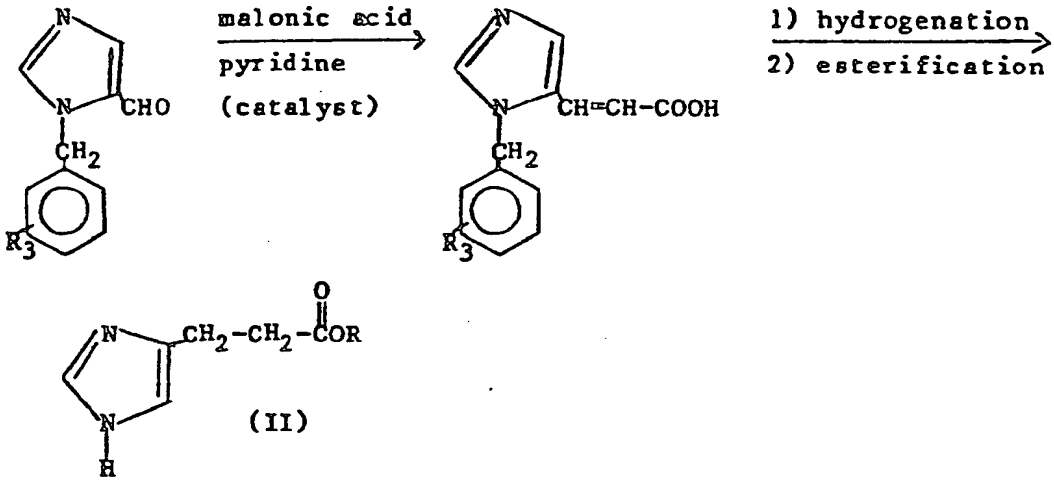
In the reaction scheme above m and n, which can be the same or different, are 0 to 2.

Choosing appropriate conditions for the dehydration of the compounds of formula (I) where R_5 is OH results in the corresponding compounds of formula (I) where one of the alkyl chains X or Y is transformed to the corresponding alkenyl chain.

In order to achieve a better control of the reactions above, as starting material may be used an amide of the 4(5)-imidazole propionic acid as well. Especially suitable in this respect is for example a piperidinyl amide of the formula

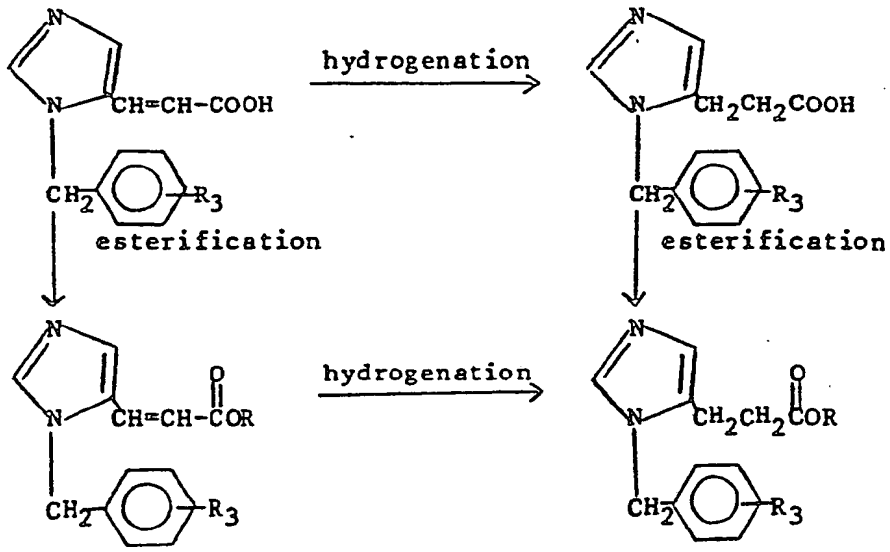


In the processes described above, the 4(5)-imidazole propionic acid esters (II) and (III) may be prepared for example starting from 1-benzyl-5-imidazole carbaldehyde and malonic acid, which are condensed together to form a 5-(1-benzylimidazole)acrylic acid. When this compound is hydrogenated under acidic conditions at elevated temperature (70-80°C) in the presence of a catalyst, 4-imidazole propionic acid is formed. The subsequent treatment with alcohol, e.g. methanol, in the presence of dry hydrochloric acid leads to 4-imidazole propionic acid alkyl ester, which is used as starting material in the Grignard reaction:

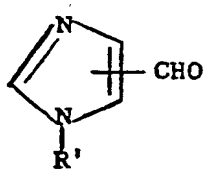


(II)

When 5-(1-benzylimidazole) acrylic acid (the benzyl group may be substituted or unsubstituted) is hydrogenated at room temperature in alcohol 1-benzyl-5-imidazole propionic acid is achieved. The following treatment with alcohol in the presence of dry hydrochloric acid at elevated temperature leads to another possible starting material for the Grignard reaction, namely 1-benzyl-5-imidazole propionic acid alkyl ester. The described reaction steps can be conducted in the opposite order as well. The reaction schemes are as follows:

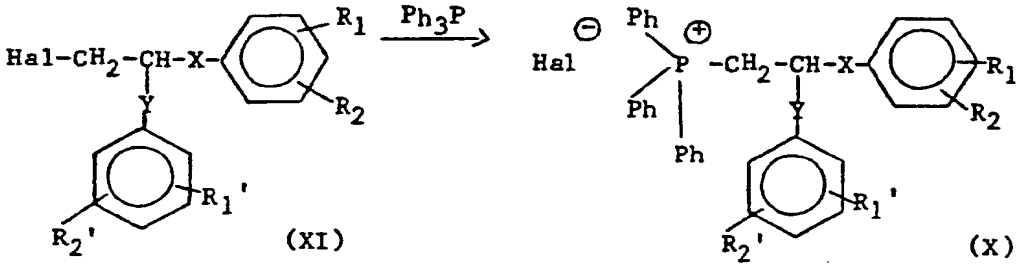


The compounds of formula (I) can be prepared by the Wittig reaction and the Grignard reaction wherein the starting compound is a 4(5)-imidazole aldehyde (IX). In the formula (IX) R' is as defined before.



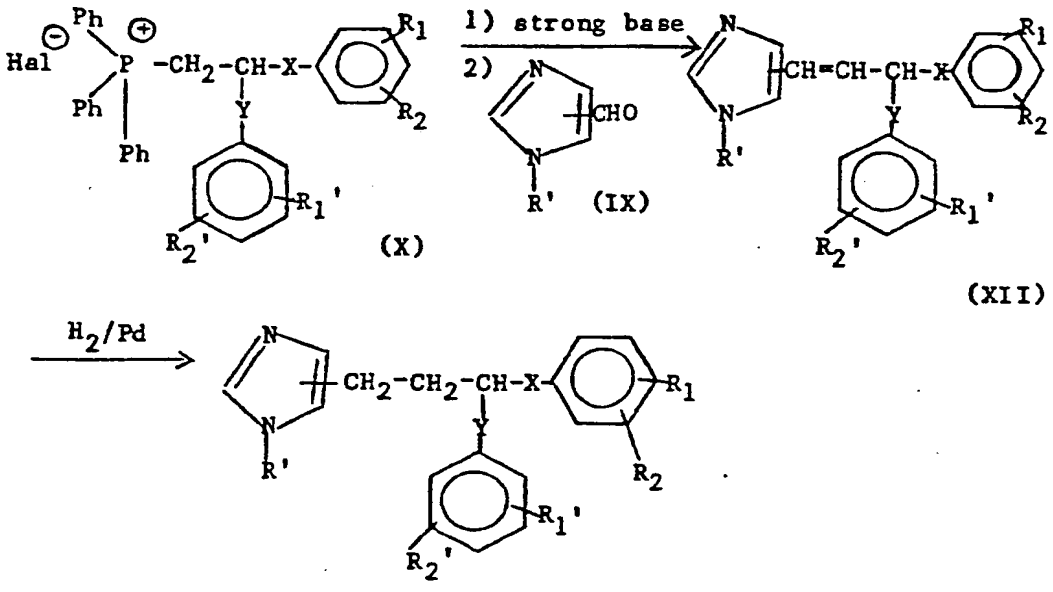
(IX)

In the Wittig reaction the first step is to prepare a phosphonium salt (X) from the corresponding halogenated hydrocarbon (XI) by reacting it with triphenylphosphine. The reaction scheme can be illustrated as follows:



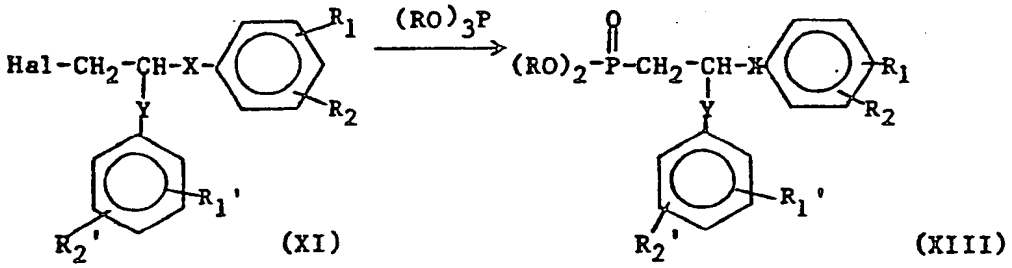
in which R'_1, R'_2, R_1, and R_2 are as hereinbefore defined.

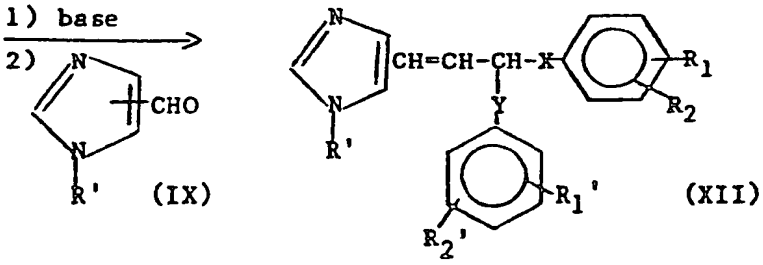
In the second step of the Wittig reaction the compound (X) is treated with a strong base to form a phosphorus ylide which is further allowed to react with the 4(5)-imidazole aldehyde (IX) to achieve the compounds of formula (I) wherein R_4 and R_6 together form a bond (XII). The strong base can be NaH or BuLi in a proper solvent such as dimethoxyethane, tetrahydrofuran or DMF. Further alkali metal alkoxides the corresponding alcohols as solvent and NaH in DMSO can be used as proton acceptors. the compounds (XII) are isolated and after that hydrogenated as has been described before to achieve the compounds of formula (I) wherein R_4 and R_6 both are hydrogen. The reaction scheme for these steps can be illustrated as follows:



The compounds of formula (I) can also be prepared by a modified Wittig reaction, namely the Horner-Emmons or Wadsworth-Emmons reaction where the phosphonate (XIII) which is prepared from th halogenated hydrocarbon (XI) and a triest r of phosphonic acid (e.g. $(EtO)_3P$) by the Arbuzow reaction reacts

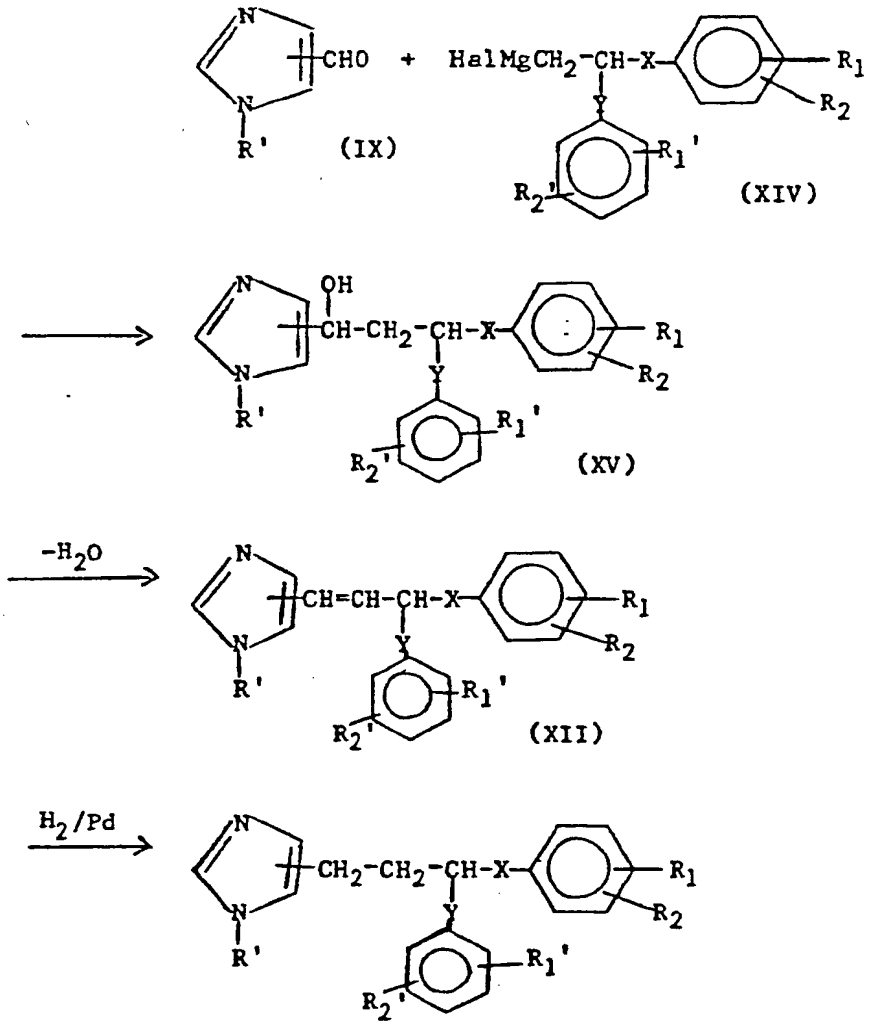
firstly with a base (e.g. NaH in DMSO or in dimethoxyethane) and then with the aldehyde (IX). The product (XII) formed is a compound of formula (I) where R_4 and R_6 together form a bond. The reaction scheme can be illustrated as follows:



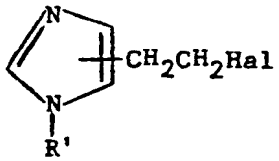


In the formula (XIII) R is alkyl with 1-4 carbon atoms and R_1, R_2, R_1', R_2', X and Y are as defined before. The unsaturated compounds (XII) are further hydrogenated to form the compounds of formula (I) wherein R_4 and R_6 both are hydrogen.

Further method to prepare the compounds of formula (I) is the Grignard reaction in which the 4(5)-imidazole aldehyde (IX) is allowed to react with a Grignard reagent (XIV) to give a compound of formula (I) where R_6 is OH (XV). The Grignard reagent is prepared by reacting the corresponding halogenated hydrocarbon with magnesium turnings in the usual way. The compound (XV) is further dehydrated by heating with $KHSO_4$ or by refluxing in acidic alcohol to achieve the compounds of formula (I) where R_4 and R_6 together form a bond (XII). The saturated derivatives are then hydrogenated to form the compounds of formula (I) wherein R_4 and R_6 both are hydrogen. The reaction scheme for these steps can be illustrated as follows:

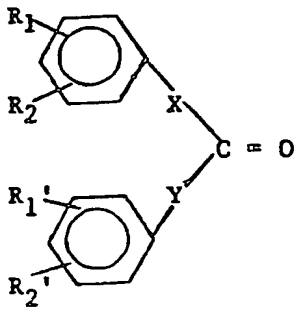


Further the compounds of formula (I) can be prepared by a Grignard reaction where the Grignard reagent (XVI) is prepared from a 4(5)-imidazolylalkylhalogenide (XVII)



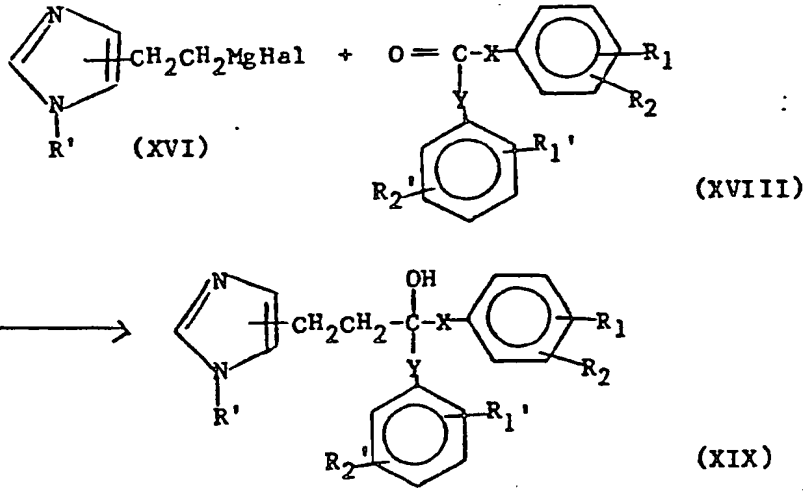
(XVII)

by allowing it to react firstly with magnesium and then with a suitable ketone (XVIII)



(XVIII)

The reaction scheme of this reaction which leads to compounds of formula (I) where R_5 is OH (XIX) can be illustrated as follows:



(XVI) (XVIII)

(XIX)

The compounds (XIX) can further be dehydrated and hydrogenated as described before to achieve the compounds of formula (I) wherein R_4 and R_5 both are hydrogen.

Administration of compounds of formula (I), their non-toxic, pharmaceutically acceptable acid salts or mixtures thereof may be achieved parenterally, intravenously or orally. typically, an effective amount of the derivative is combined with a suitable pharmaceutical carrier. As used herein, the term "effective amount" encompasses those amounts which yield the desired activity without causing adverse side-effects. The precise amount employed in a particular situation is dependent upon numerous factors such as method of administration, type of mammal, condition for whcih the derivative is administered, etc., and of course the structure of the derivative.

The pharmaceutical carriers which are typically employed with the derivatives of the present invention may be solid or liquid and are generally selected with the planned manner of administration in mind. Thus, for example, solid carriers include lactose, sucrose, gelatin and agar, while liquid carriers include water, syrup, peanut oil and olive oil. Other suitable carriers are well-known to those skilled in the art of pharmaceutical formulations. The combination of the derivative and the carrier may be fashioned into numerous acceptable forms, such as tablets, capsules, suppositories, solutions, emulsions, and powders.

The compounds of the invention are especially valuable as aromatase inhibiting agents and are therefore useful in the treatment of estrogen dependent diseases, e.g. breast cancer.

Estrogens are essential steroids in the physiology and function of normal development of breast and sex organs in women. On the other hand estrogens are known to stimulat the growth of estrogen dependent cancers, especially breast and endometrial cancers, and they may increase the risk of development of breast cancer if given at pharmacological doses for a long time.

Exc ssive production of estradiol may also cause other, benign disorders in hormone dependent organs.

The importance of estrogens as cancer growth stimulators and/or regulators is clearly stressed by the fact that antiestrogens have reached a central position in the treatment of estrogen receptor rich breast cancers. Antiestrogens act by binding to estrogen receptors and thereby inhibiting the biological effects of estrogens. Another approach for blocking estrogen effect is to inhibit the synthesis of strogens. This has been achieved clinically by the unspecific steroid synthesis inhibitor aminoglutethimide. The estrogen synthesis could be blocked specifically by inhibiting the enzyme aromatase, which is the key enzyme in biochemical estrogen synthesis pathway. Aromatase inhibition seems highly promising because several breast tumours synthesise estradiol and estrone in situ and exhibit therefore continuous growth stimulation (Alan Lipton et al., Cancer 59: 779-782, 1987).

The ability of the compounds of the invention to inhibit the enzyme aromatase was shown by the in vitro assay method according to M. Pasanen, Biological Research in Pregnancy, vol. 6, No. 2, 1985 (pp. 94-99). Human aromatase enzyme was used. The enzyme was prepared from human placenta, which is rich in the enzyme. Microsomal fraction (100000 x g precipitate) was prepared by centrifugation. The enzyme preparation was used without further purification. Test compounds listed in Table 1 were added with 100000 dpm of 1,2[^{3}H]-androstene-3,17-dione and NADPH generating system. The concentrations of the test compounds were 0,001; 0,01; 0,1 and 1,0 mM. The incubation was carried out at 37°C for 40 min. Aromatization of 1,2[^{3}H]-androstene-3,17-dione results in the production of ^3H_2O. The tritiated water and the tritiated substrate are easily separated by a Sep-Pak® minicolumn, which absorbs the steroid but allows free water elution. Radioactivity was counted by a liquid scintillation counter. Aromatase inhibition was evaluated by comparing the ^3H_2O-radioactivity of inhibitor treated samples to controls containing no inhibitor. IC-10, IC-50 and IC-90 values were calculated as concentrations whcih inhibited the enzyme activity 10%, 50% and 90%, respectively. These concentrations are presented in Table 2.

Table 1

Compounds tested

No.	Name
1.	4-[5-(2,6-dimethylphenyl)-3-hydroxy-3-(2,6-dimethylphenylethyl)-pentyl]-1H-imidazole
2.	4-[3,3-bis(4-chlorophenyl)-3-hydroxypropyl]-1H-imidazole
3.	4-(3,3-diphenyl-3-hydroxypropyl)-1H-imidazole
4.	4-(3,3-diphenylpropen-2-yl)-1H-imidazole
5.	4-(3,3-diphenylpropyl)-1H-imidazole
6.	4-[3,3-bis(2-methylphenyl)-3-hydroxypropyl]-1H-imidazole
7.	4-[3,3-bis(4-chlorophenyl)propen-2-yl]-1H-imidazole
8.	4-[3,3-bis(2-methylphenyl)propen-2-yl]-1H-imidazole
9.	4-[3,3-bis(2-methylphenyl)propyl]-1H-imidazole
10.	1-benzyl-5-(3,3-diphenylpropyl)-1H-imidazole
11.	4-[3,3-bis(3-methylphenyl)propyl]-1H-imidazole
12.	4-[3,3-bis(3-methylphenyl)propen-2-yl]-1H-imidazole
13.	4-[3,3-bis(3-methoxyphenyl)propyl]-1H-imidazole
14.	4-[3,3-bis(2,3-dimethylphenyl)propyl]-1H-imidazole
15.	1-benzyl-5-[3,3-bis(3-methoxyphenyl)propyl]-1H-imidazole
16.	1-benzyl-5-[3,3-bis(3-methoxyphenyl)propen-2-yl]-1H-imidazole
17.	4-[3,3-bis(3,5-dimethylphenyl)propyl]-1H-imidazole
18.	4-[3,3-bis(4-methylphenyl)propyl]-1H-imidazole
19.	4-[3,3-bis(3-fluorophenyl)propyl]-1H-imidazole
20.	1-benzyl-5-(3,3-diphenylpropen-2-yl)-1H-imidazole

Table 2

Inhibition of human aromatase by test compounds. IC-10, IC-50 and IC-90 represent the concentration which inhibit the enzyme by 10%, 50 % and 90 %, respectively

Compound No.	IC-10 mmol/l	IC-50 mmol/l	IC-90 mmol/l
1	0,02	1,0	> 1
2	0,004	0,06	1,0
3	0,004	0,07	1,0
4	< 0,001	0,006	0,10
5	0,0015	0,015	0,40
6	0,015	0,30	> 1
7	0,002	0,030	0,6
8	0,0015	0,080	> 1
9	0,002	0,030	0,6
10	~ 0,0006	0,004	0,10
11	~ 0,0006	0,006	0,10
12	0,001	0,080	1
13		0,003	
14		0,044	
15		0,004	
16		0,014	
17		0,130	
18		0,014	
19		0,019	
20		0,050	

The daily dose for a patientvaries from about 20 to about 200 mg, administered orally.

The toxicity of the imidazole derivatives of the present invention was studied in rats. There were 5 female rats in each drug group and dosing was carried out during 8 days. The dose level used was 10 mg/kg/day orally. The derivatives tested were 4-(3,3-diphenylpropen-2-yl)-1H-imidazole, 4-(3,3-diphenylpropyl)-1H-imidazole, 4-[3,3-bis(2-methylphenyl)propyl]-1H-imidazole, 1-benzyl-5-(3,3-diphenylpropyl)-1H-imidazole and 1-benzyl-5-(3,3-diphenylpropen-2-yl)-1H-imidazole.

The behaviour, appearance and mortality of the animals were followed daily. The animals were weighed before and after dosing period. The organs were examined macroscopically at autopsy. The liver, uterus and ovaries were weighed. No mortality were observed. The weight development was normal in all groups. In the groups that were treated with 4-(3,3-diphenylpropen-2-yl)-1H-imidazole and 1-benzyl-5-(3,3-diphenylpropen-2-yl)-1H-imidazole a slight piloerection was observed propably as pharmacological effects of the drugs. No drug-related findings were observed in organ weights or in macroscopical pathology. In conclusion, all studied compounds were well tolerated.

The following examples illustrate the invention.

Example 1

4-(3,3-diphenyl-3-hydroxypropyl)-1H-imidazole

a) 5-(1-benzylimidazole)acrylic acid

In a flask are placed 18,6 g of 5-(1-benzylimidazole)-carbaldehyde, 10,4 g of malonic acid, and 4,8 ml of pyridine. The mixture is heated on a boiling water bath for 16 hours. It is then cooled and diluted with water. The precipitate which is the product is filtered and washed with water. Yield 15 g. M.p.221-226°C.
^{1}H NMR: 5.15 (s, 1H), 5.64 (s, 2H), 6.58 (d, 1H), 7.3-7.5 (m, 5H), 7.61 (d, 1H), 8.08 (s, 1H), 9.07 (s, 1H)

b) 4(5)-imidazole propionic acid ethyl ester

5-(1-benzylimidazole)acrylic acid (15 g) is dissolved in 50 ml of 4-N hydrochloric acid. About 60 mg of 10 % Pd/C are added and the mixture is stirred vigorously under a hydrogen atmosphere at about 85° C until no more hydrogen is consumed. The reaction mixture is then filtered and evaporated to dryness.

The residue is dissolved in 50 ml of abs. ethanol and dry hydrogen chlorid gas is passed into the solution for 4 hours during which time th reaction mixture is maintained at reflux with stirring. The mixture is then evaporat d to dryness to give an oily residue which is a crude product useful as such in the following Grignard reaction.

^{1}H NMR: 1.237 (t, 3H), 2.656 (t, 2H), 2.936 (t, 2H), 4.137 (q, 2H), 6.804 (s, 1H), 7.559 (s, 1H)

c) 4-(3,3-diphenyl-3-hydroxypropyl)-1H-imidazole

3,3 g of magnesium turnings are covered with 100 ml of dry tetrahydrofuran. To that mixture is then added dropwise a solution of 21,8 g of bromobenzene in 30 ml of dry tetrahydrofuran at such a rate that a smooth reaction is maintained. After the addition is complete, the reaction mixture is refluxed for one additional hour and cooled to room temperature. The reaction mixture is then added dropwise to a solution of 4(5)-imidazole propionic acid ethyl ester (7,8 g) in 50 ml of tetrahydrofuran at room temperature. After the addition is complete, the reaction mixture is stirred for an additional hour at 40-50°C. The mixture is then cooled and poured into cold water. Tetrahydrofuran is evaporated and to the solution is added conc. hydrochloric acid (20 ml). The solution is cooled and the precipitate which contains the product as hydrochloride salt is removed by filtration, washed and dried. Yield 11,2 g. M.p. 189-191°C.

^{1}H NMR: 2.703 (s, 4H), 4.758 (s, 3H), 7.214-7.429 (m, 11H), 8.457 (s, 1H)

In the same way, via the Grignard reaction starting from 4(5)-imidazole propionic acid ethyl ester and from proper substituted bromobenzene, can also be prepared other compounds of the invention.

For example the following substituted derivatives were prepared:

4-[3,3-bis(4-chlorophenyl)-3-hydroxypropyl]-1H-imidazole. M.p. of hydrochloride 85-89°C.

4-[3,3-bis(2-methylphenyl)-3-hydroxypropyl]-1H-imidazole. M.p. of hydrochloride 211-213°C.

4-[3,3-bis(3-methylphenyl)-3-hydroxypropyl]-1H-imidazole. M.p. of hydrochloride 170-172°C.

Example 2

4-(3,3-diphenylpropen-2-yl)-1H-imidazole

2,0 g of 4-(3,3-diphenyl-3-hydroxypropyl)-1H-imidazole hydrochloride is mixed with 20 g of anhydrous potassium hydrogen sulfate and the mixture is warmed on an oil bath at 150-155°C for 4 hours. The mixture is then cooled and 20 ml water is added. The mixture is made alkaline with sodium hydroxide solution and cooled. The precipitate, which is the product, is filtered, washed with water and dried. Yield 1,25 g. After recrystallization from water-ethanol, the product melts at 124-128°C.

^{1}H NMR: 3.42 (d, 2H), 4.756 (s, 1H), 6.284 (t, 1H), 6.768 (s, 1H), 7.2-7.4 (m, 10H), 7.559 (s, 1H)

According to the same procedure for example the following substituted derivatives were prepared:

4-[3,3-bis(4-chlorophenyl)propen-2-yl]-1H-imidazole hydrochloride M.p. 158-163°C.

4-[3,3-bis(2-methylphenyl)propen-2-yl]-1H-imidazole hydrochloride. M.p. 195-198°C.

4-[3,3-bis(3-methylphenyl)propen-2-yl]-1H-imidazole. M.p. 115-118°C.

4-[3,3-bis(3-fluorophenyl)propen-2-yl]-1H-imidazole. M.p. of hydrochloride is 125-128°C.

Example 3

4-(3,3-diphenylpropyl)-1H-imidazole

4-(3,3-diphenylpropen-2-yl)-1H-imidazole (0,7 g) is dissolved in ethanol and a catalytic amount of Pd/C (10 %) is added. The reaction mixture is agitated vigorously at room temperature in a hydrogen atmosphere until the uptake of hydrogen ceases. The mixture is filtered and the filtrate is evaporated to dryness. The residue is recrystallized from water-ethanol mixture. Yield 0,4 g, m.p. 115-117°C.

^{1}H NMR: 2.3-2.5 (m, 4H), 3.919 (t, 1H), 4.752 (s, 1H), 6.708 (s, 1H), 7.1-7.3 (m, 10H), 7.532 (s, 1H)

According to the same procedure as the example the following substituted derivatives were prepared:

4-[3,3-bis(2-methylphenyl)propyl]-1H-imidazole, hydrochloride. M.p. 84-87°C.

4-[3,3-bis(3-methylphenyl)propyl]-1H-imidazole. M.p. 111-114°C.

^{1}H NMR (as base):

2.272 (s, 6H), 2.2-2.5 (m, 4H), 3.823 (t, 1H), 6.691 (s, 1H), 6.8-7.2 (m, 8H), 7.440 (s, 1H).

4-[3,3-bis(3-fluorophenyl)propyl]-1H-imidazole

^{1}H NMR (as HCl):

2.3-2.8 (m, 4H), 4.060 (t, 1H), 4.784 (s, 2H), 6.7-7.4 (m, 9H), 8.743 (s, 1H)

Example 4

1-benzyl-5-[3,3-bis(4-chlorophenyl)-3-hydroxypropyl]-1H-imidazole

a) 1-benzyl-5-imidazole acrylic methyl ester

In a flask are placed 12,0 g of 5-(1-benzylimidazole)acrylic acid (prepared in example 1), 70 ml of methanol and dry hydrogen chloride gas is passed into the solution for 4 hours, during which time the reaction mixture is maintained at reflux. The mixture is then vaporated to dryness and the residue is dissolved in cold water. The solution is then made alkaline with sodium carbonate and the precipitate, which is the product, is filtered, washed with water and dried. Yield 12,2 g; m.p. 137-139°C.

^{1}H NMR: 3.781 (s, 3H), 5.490 (s, 2H), 6.462 (d, 1H), 7.2-7.5 (m, 5H), 7.493 (d, 1H), 7.710 (s, 1H), 8.083 (s, 1H)

b) 1-benzyl-5-imidazol propionic acid methyl ester

The double bond of the side chain is hydrogenated in abs. ethanol Pd/C as catalyst. When the uptake of hydrogen ceases, the reaction mixture is filtered and the filtrate is evaporated to dryness. The residue is dissolved in methylene chloride, which is washed with water. Methylene chloride phase is then dried and evaporated to dryness to give the product, which is used as such in the accompanying Grignard reactions. ^{13}C NMR: Aliphatic carbons are detected at ppm: 19.374, 32.573, 48.466, 51.675; aromatic carbons are detected at ppm: 126.569, 128.022, 128.748, 128.960, 130.474, 136.074, 137.88; and carbonyl at ppm: 172/522

c) 1-benzyl-5-[3,3-bis(4-chlorophenyl)-3-hydroxypropyl]-1H-imidazole

The Grignard reagent is prepared from 2,4 g of magnesium turnings and from 19,1 g of p-chlorobromobenzene in tetrahydrofuran as is described in Example 1 c).

1-benzyl-5-imidazole propionic acid methyl ester (6,4 g) in tetrahydrofuran is heated at 60° C and to this is then added dropwise p-chlorophenylmagnesium bromide prepared above. After the addition is complete, the reaction mixture is refluxed for an additional 3 hours, cooled and poured into cold water. Tetrahydrofuran is evaporated, toluene is added and the mixture is made acidic with hydrochloric acid. The precipitated product is filtered, washed with ether and dried. Yield 12,2 g; m.p. 210-213° C. M.p. of nitrate 157-160° C (made in water-ether mixture). M.P. of hydrochloride (from ethylacetate) 178-187° C.

^1H-NMR: 2.985 (s, 4H), 4.854 (s, 2H), 5.330 (s, 2H), 7.06-7.46 (m, 14H), 8.993 (s, 1H)

Other 1-benzyl substituted derivatives are also prepared in the same way. For example:
1-benzyl-5-[5-(2,6-dimethylphenyl)-3-hydroxy-3-(2,6-dimethylphenylethyl)pentyl]-1H-imidazole from 1-benzyl-5-imidazole propionic acid methyl ester and 2-(2,6-dimethylphenyl)ethylmagnesium bromide. Melting point of the hydrochloride is 67-71° C.

Example 5

1-benzyl-5-[3,3-bis(4-chlorophenyl)propen-2-yl]-1H-imidazole

4,1 g of 1-benzyl-[3,3-bis(4-chlorophenyl)-3-hydroxypropyl]-1H-imidazole and 22,0 g of anhydrous potassium hydrogen sulfate are heated at 150° C for 4 hours. The mixture is cooled, 100 ml of ethanol is added to dissolve the product. The mixture is then filtered and the filtrate is evaporated to minor volume. Water is added and the mixture is made basic with sodium hydroxide. The precipitate, which is the product, is filtered, washed with water and dried. The product is recrystallized from water-ethanol. Yield 2,3 g. Nitrate is made in water with nitric acid.

^1H NMR: 3,293 (d, 2H), 5.287 (s, 1H), 6.010 (t, 1H), 6.9-7.4 (m, 14H), 9.330 (s, 1H)

Example 6

4-[3-(4-chlorophenyl)-3-hydroxy-3-phenylpropyl]-1H-imidazole

a) 3-(4-imidazolyl)propyl 4-chlorophenyl ketone

0,85 g of magnesium turnings are covered with 20 ml of dry tetrahydrofuran, the mixture is heated to boiling and to it is added 6,8 g of 4-bromochlorobenzene in tetrahydrofuran at such a rate that a smooth reaction is maintained. After the addition is complete, the reaction mixture is refluxed for one additional hour. The reaction mixture is then cooled and added dropwise at room temperature to a solution of 4(5)-imidazole propionic acid ethyl ester (4,0 g) in tetrahydrofuran. After addition the reaction mixture is stirred for an additional hour at room temperature. It is then poured into cold water and made acidic with hydrochloric acid. The reaction mixture is then washed with methylene chloride, made alkaline with sodium hydroxide, and the product is extracted to methylene chloride. Yield 2,2 g. Hydrochloride salt is made in conc. hydrochloric acid. M.p. 160-161° C.

b) 4-[3-(4-chlorophenyl)-3-hydroxy-3-phenylpropyl]-1H-imidazole

Phenylmagnesiumbromide is made in tetrahydrofuran from 0,51 g of magnesium turnings and 3,3 g of bromobenzene. 3-(4-imidazolyl)propyl 4-chlorophenyl ketone (2,3 g) is dissolved in tetrahydrofuran and phenylmagnesiumbromide is dropped to that solution at room temperature. After addition the reaction mixture is stirred at 40-50° C for additional 3 hours. It is then cooled and poured into cold water. Water is made acidic with hydrochloric acid. The product is extracted into methylenechloride, which is evaporated into dryness. The product as hydrochloride is recrystallized from water-ethanol. Yield 3,2 g.

Example 7

1-benzyl-4-(3,3-diphenylpropyl)-1H-imidazole and 1-benzyl-5-(3,3-diphenylpropyl)-1H-imidazole

4-(3,3-diphenylpropyl)-1H-imidazole (2,6 g) is dissolved in 6 ml of dry dimethylformamide. While stirring 0,5 g of NaH (60%) is added during half an hour at room temperature. Aft r addition the reaction mixture is stirred additional one hour. 1,7 g of benzylbromide in 3 ml of dim thylformamide is then dropped at room temperature and stirring is continu d for 4 hours. Th reaction mixtur is poured to cold water (30 ml) and the mixture is extracted with toluene. Toluene extracts are then washed with water and evaporated to dryness. The residue, which is the mixture of products, is purified and separated to pur isomers by column chromatogrpahy

(methylene chloride/methanol, 9,5/0,5).
^{1}H NMR of the products:
One of the isomers:
2.57 (m, 4H), 3.52 (1H), 3,877 (t, 1H), 5.362 (s, 2H), 6.531 (s, 1H), 7.05-7.40 (m, 15H), 9.567 (s, 1H)
The other isomer:
2.375 (m, 4H), 3,858 (t, 1H), 5.253 (s, 2H), 7.01-7.36 (m, 16H), 9.441 (s, 1H)

Example 8

1-(4-chlorobenzyl)-4-(3,3-diphenylpropyl)-1H-imidazole and
1-(4-chlorobenzyl)-5-(3,3-diphenylpropyl)-1H-imidazole
The compounds were prepared in the same way as the compounds in Example 7 starting from 4-(3,3-diphenylpropyl)-1H-imidazole and 4-chlorobenzylchloride.
^{1}H NMR of the products:
One isomer:
2.48 (m, 4H), 3.934 (t, 1H), 4.999 (s, 2H), 6.514 (s, 1H), 7.0-7.3 (m, 14H), 7.517 (s, 1H)
The other isomer:
2.33 (m, 4H), 3.887 (t, 1H), 4.852 (s, 2H), 6.7-7.5 (m, 16H)

Exmaple 9

4-[5-(2,6-dimethylphenyl)-3-(2,6-dimethylphenylethyl)pentyl]-1H-imidazole
4,0 g of 1-benzyl-5-[5-(2,6-dimethylphenyl)-3-hydroxy-3-(2,6-dimethylphenylethyl)pentyl]-1H-imidazole hydrochloride and 20 g of kalium hydrogen sulfate is combined and the mixture is heated for 6 hours at 150° C. Ethanol (40 ml) is added and the mixture is filtered. 20 ml of conc. hydrochloric acid is added and the mixture is hydrogenated palladium on carbon (10 %) as catalyst until the hydrogen consumption ceases. The reaction mixture is filtered, water is added and the mixture is made alkaline with sodium hydroxide. The product is then extracted into toluene, which is washed with water, and evaporated to dryness. The residue, which is the product as base, is converted to nitrate with nitric acid in water. M.p. 147-150° C.

Example 10

4-[3,3-bis(3,5-dimethylphenyl)propyl]-1H-imidazole

a) 1-benzyl-5-[3,3-bis(3,5-dimethylphenyl)-3-hydroxypropyl]-1H-imidazole
1,06 g of magnesium turnings are covered with 30 ml of dry tetrahydrofuran. To the mixture is then added dropwise a solution of 5-bromo-m-xylene (8,14 g) in 10 ml of dry tetrahydrofuran at such a rate that a smooth reaction is maintained. After the addition is complete, the reaction mixture is refluxed for one additional hour and cooled to room temperature. The reaction mixture is then added dropwise to a solution of 1-benzyl-5-imidazole propionic acid ethyl ester (5,0 g) in 40 ml of tetrahydrofuran at 60° C. After the addition is complete, the reaction mixture is refluxed for 2 hours, cooled and poured into cold water. Tetrahydrofuran is evaporated and to the solution is added conc. hydrochloric acid. The solution is cooled, some ether is added and the precipitate which contains the product as hydrochloride salt is removed by filtration, washed and dried. Yield 4,1 g. M.p. 120-124° C.

b) 1-benzyl-5-[3,3-bis(3,5-dimethylphenyl)propen-2-yl]-1H-imidazole
4,0 g of 1-benzyl-5-[3,3-bis(3,5-dimethylphenyl)-3-hydroxypropyl]-1H-imidazole is dissolved in 30 ml of ethanol and 2 ml of conc. hydrochloric acid is added. The reaction mixture is then refluxed for 4 hours and evaporated to dryness. The residue which is the product is recrystallized from ethyl acetate. Yield 3,1 g M.p. 170-176° C.
According to the same procedure as the example the following substituted derivatives were prepared:
1-benzyl-5-(3,3-diphenylpropen-2-yl)-1H-imidazole, hydrochloride M.P. 173-175° X.
1-benzyl-5-[3,3-bis(2-methoxyphenyl)propen-2-yl]-1H-imidazole, hydrochloride. M.p. 191-194° C.
1-benzyl-5-[3,3-bis(3-methoxyphenyl)propen-2-yl]-1H-imidazole, hydrochloride. M.p. 132-135° C.
1-benzyl-5-[3,3-bis(4-methoxyphenyl)propen-2-yl]-1H-imidazole, hydrochloride. M.p. 157-163° C.
1-benzyl-5-[3,3-bis(2,3-dimethylphenyl)propen-2-yl]-1H-imidazole, hydrochloride.
^{1}H NMR (as base):
2.055 (s, 3H), 2.159 (s, 3H), 2.251 (s, 6H), 3.467 (d, 2H), 4.781 (s, 1H), 5.281 (s, 2H), 5.761 (t, 1H), 6.8-7.4 (m, 12H), 9.97 (s, 1H)
1-benzyl-5-[3,3-bis(2-methylphenyl)propen-2-yl]-1H-imidazole, hydrochloride. m.p. 84-87° C.
1-benzyl-5-[3,3-bis(3-methylphenyl)propen-2-yl]-1H-imidazole, hydrochloride. M.p. 115-117° C.

c) 1-benzyl-5-[3,3-bis(3,5-dimethylphenyl)propyl]-1H-imidazole
1-benzyl-5-[3,3-bis(3,5-dimethylphenyl)propen-2-yl]-1H-imidazole hydrochlorid is dissolved in thanol and a catalytic amount of Pd/C (10 %) is added. The reaction mixture is agitated vigorously at room temperature in

a hydrogen atmospher until the uptak of hydrogen ceases. The mixtur is filtered and the filtrate is evaporated to dryness. The residue which is the product is purified by flash chromatography eluating with methylene chloride-methanol mixture.

By the sam method is prepared for exmaple 1-benzyl-5-[3,3-bis(3-methoxyphenyl)propyl]-1H-imidazole hydrochloride, m.p. 165-167°C, and 1-benzyl-5-[3,3-diphenylpropyl]-1H-imidazole hydrochloride, m.p. 160-162°C.

d) 4-[3,3-bis(3,5-dimethylphenyl)propyl]-1H-imidazole

2,0 g of 1-benzyl-5-[3,3-bis(3,5-dimethylphenyl)propyl]-1H-imidazole hydrochloride is hydrogenated in the mixture of 30 ml of 2 N hydrochloric acid and 10 ml ethanol at 80°C Pd/C (10 %) as catalyst. When the uptake of hydrogen ceases, the reaction mixture is cooled, filtered and evaporated to dryness. Water is added and the mixture is made alkaline with sodium hydroxide. The product is then extracted to ethylacetate which is washed with water, dried with sodium sulfate and evaporated to dryness. The residue is the product as base and it is made to its hydrochloride salt in ethyl acetate using dry hydrochloric acid. Yield 0,6 g. M.p. of the product is 101-105°C.

^{1}H NMR: 2.247 (s, 12H), 2.2-3.7 (m, 4H), 3.798 (t, 1H), 4.788 (s, 2H), 6.8-7.2 (m, 6H), 7.214 (s, 1H), 8.715 (s, 1H)

Using the same method for example the following compounds included in the invention were prepared:

4-[3,3-bis(2,3-dimethylphenyl)propyl]-1H-imidazole

^{1}H NMR (as base):

2.097 (s, 6H), 2.260 (s, 6H), 2.3 (m, 2H), 2.6 (m, 2H), 4.389 (s, 1H), 6.0 (s, 1H), 6.712 (s, 1H), 7.011 (s, 6H), 7.508 (s, 1H)

4-[3,3-bis(2-methoxyphenyl)propyl]-1H-imidazole, hydrochloride. M.p. 194-196°C.

4-[3,3-bis(3-methoxyphenyl)propyl]-1H-imidazole

^{1}H NMR (as base):

2.5 (m, 4H), 3.747 (s, 6H), 3.862 (t, 1H), 6.6-7.3 (m, 9H), 7.498 (s, 1H), 8.165 (s, 1H)

4-[5-(2,6-dimethylphenyl)-3-hydroxy-3-(2,6-dimethylphenylethyl)pentyl]-1H-imidazole, hydrochloride. M.p. 178-180°C.

4-[3,3-bis(4-methoxyphenyl)propyl]-1H-imidazole

^{1}H NMR (as base):

2.5 (m, 4H), 3.744 (s, 6H), 3.815 (t, 1H), 6.1 (broad signal, 1H), 6.732-7.171 (m, 9H), 7.489 (s, 1H)

4-[3,3-bis(4-methylphenyl)propyl]-1H-imidazole

^{1}H NMR (as hydrochloride):

2.260 (s, 6H), 2.5 (m, 4H), 3.879 (t, 1H), 4.907 (s, 2H), 6.9-7.2 (m, 9H), 8.727 (s, 1H)

Example 11

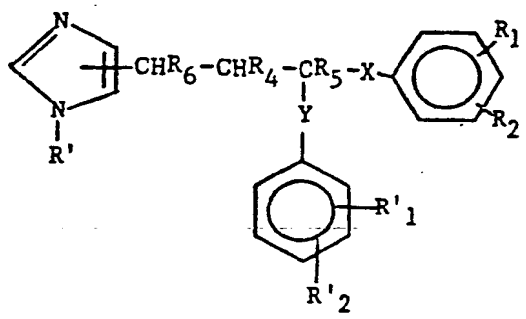
1-benzyl-5-[3,3-bis(4-methylphenyl)propen-2-yl]-1H-imidazole

To a dry flask is placed 4,8 g (0,2 mol) of NaH (washed free from oil with cyclohexane). Onto it is then dropped 100 ml of dry dimethylsulfoxide. The reaction vessel is warmed at 80°C until the evolution of hydrogen ceases. The resulting solution of methylsulfinyl carbanion is cooled in an ice-water bath and 54,1 g of 3-(1-benzyl-5-imidazolyl)-propyltriphenylphosphonium bromide is added in 200 ml of dimethylsulfoxide. The reaction mixture is then stirred at room temperature for 0,5 hours and to it is added in small portions 23,0 g of 4,4'-dimethylbenzophenone. The reaction mixture is stirred at room temperature for 1 hour and some of the dimethylsulfoxide is distilled. The residue is poured into water which is made alkaline with sodium hydroxide. The product is extracted into toluene which is washed with water, dried with sodium sulfate and evaporated to dryness. From the residue which contains the crude product as base is converted into the hydrochloride in ethylacetate. Yield 32 g. M.p. 216-220°C.

^{1}H NMR: 2.289 (s, 3H), 2.370 (s, 3H), 3.467 (d, 2H), 4.764 (s, 1H), 5.302 (s, 2H), 6.030 (t, 1H), 6.8-7.4 (m, 9H), 8.9 (s, 1H)

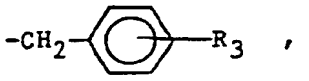
Claims

1. A substituted imidazole of the formula



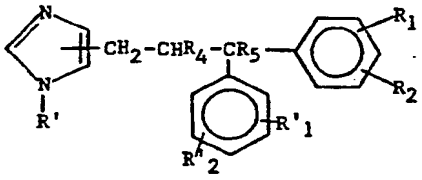
(I)

or a non-toxic pharmaceutically acceptable acid addition salt thereof wherein R_1, R_2, R'_1 and R'_2, which can be the same or different, are H, CH_3 C_2H_5, OCH_3, OH, CH_2OH, NH_2 or halogen; R' is H or



where R_3 is H, CH_3 or halogen; R_4 is H, R_5 is H or OH and R_6 is H or OH or one of R_5 and R_6 is H and the other, together with R_4, forms a bond and X and Y, which can be the same or different, are a bond, a straight C_{1-2}-alkyl or the corresponding alkenyl.

2. A substituted imidazole of the formula



or a non-toxic pharmaceutically acceptable acid addition salt thereof wherein R_1, R_2, and R'_1 and R'_2 which can be the same or different are H, CH_3, C_2H_5, OCH_3, OH, CH_2OH, NH_2 or halogen; R' is H or

where R_3 is H, CH_3 or halogen; R_4 is H and R_5 is H or R_4 and R_5 together form a bond.

3. A substituted imidazole according to claim 2 wherein R_4 and R_5 are both H.

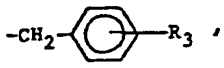
4. A substituted imidazole according to claim 2 wherein R_4 and R_5 together form a bond.

5. A substituted imidazole according to claim 2 3 or 4 wherein at least one of R_1, R_2, R'_1 and R'_2 is not H and one or more of the substituents R_1, R_2, R'_1 and R'_2 are in the 3, 5, 3' or 5' positions of the phenyl groups.

6. A substituted imidazole according to claim 5 wherein R_2 and R'_2 both are H and R_1 and R'_1 are both not H and are both in the meta position of the phenyl groups.

7. A substituted imidazole according to any one of claims 2 to 6 wherein R' is H.

8. A substituted imidazole according to any on of claims 2 to 6 wherein R' is



where R_3 is H, CH_3 or halogen.

9. A substituted imidazole according to claim 8 wherein R_3 is H.

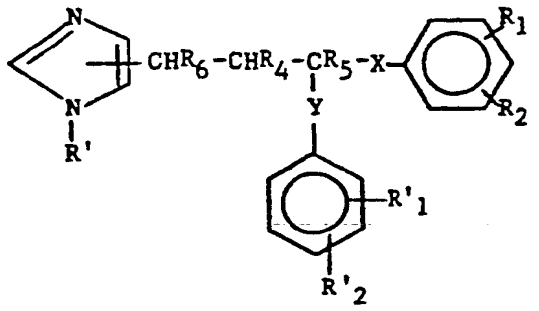
10. A compound according to claim 1 which is 4-[5-(2,6-dimethylphenyl)-3-hydroxy-3-(2,6-dimethylphenylethyl)pentyl]-1H-imidazole,
4-[3,3-bis(4-chlorophenyl)-3-hydroxypropyl]-1H-imidazole,
4-[3,3-diphenyl-3-hydroxypropyl)-1H-imidazole,
4-(3,3-diphenylpropen-2-yl)-1H-imidazole,
4-(3,3-diphenylpropyl)-1H-imidazole,
4-[3,3-bis(2-methylphenyl)-3-hydroxypropyl]-1H-imidazole,
4-[3,3-bis(4-chlorophenyl)propen-2-yl]-1H-imidazole,
4-[3,3-bis(2-methylphenyl)propen-2-yl]-1H-imidazole,
4-[3,3-bis(2-methylphenyl)propyl]-1H-imidazole,
1-benzyl-4-(3,3-diphenylpropyl)-1H-imidazole,
1-benzyl-5-(3,3-diphenylpropyl)-1H-imidazole,
4-[3,3-bis(3-methylphenyl)propyl]-1H-imidazole,
4-[3,3-bis(3-methylphenyl)propen-2-yl]-1H-imidazole,
1-(4-chlorobenzyl)-4-(3,3-diphenylpropyl)-1H-imidazole,
1-(4-chlorobenzyl)-5-(3,3-diphenylpropyl)-1H-imidazole,
4-[5-(2,6-dimethylphenyl)-3-(2,6-dimethylphenylethyl)pentyl]-1H-imidazole,
4-[3,3-bis(3,5-dimethylphenyl)propyl]-1H-imidazole,
4-[3,3-bis(3-methoxyphenyl)propyl]-1H-imidazole,
4-[3,3-bis(2,3-dimethylphenyl)propyl]-1H-imidazole,
1-benzyl-5-[3,3-bis(3-methoxyphenyl)propyl]-1H-imidazole,
1-benzyl-5-[3,3-bis(3-methoxyphenyl)propen-2-yl]-1H-imidazole,
4-[3,3-bis(3,5-dimethylphenyl)propyl]-1H-imidazole,
4-[3,3-bis(4-methylphenyl)propyl]-1H-imidazole,
4-[3,3-bis(3-fluorophenyl)propyl]-1H-imidazole,
1-benzyl-5-[3,3-bis(4-chlorophenyl)-3-hydroxypropyl]-1H-imidazole,
1-benzyl-5-[3,3-bis(4-chlorophenyl)propen-2-yl]-1H-imidazole,
4-[3-(4-chlorophenyl)3-hydroxy-3-phenylpropyl]-1H-imidazole,
4-[3,3-bis(3-methylphenyl)-3-hydroxypropyl]-1H-imidazole,
4-[3,3-bis(3-fluorophenyl)propen-2-yl]-1H-imidazole,
1-benzyl-5-[5-(2,6-dimethylphenyl)-3-hydroxy-3-(2,6- dimethylphenylethyl)-pentyl]-1H-imidazole,
1-benzyl-5-[3,3-bis(3,5-dimethylphenyl)-3-hydroxypropyl]-1H-imidazole,
1-benzyl-5-[3,3-bis(3,5-dimethylphenyl)propen-2-yl]-1H-imidazole,
1-benzyl-5-[3,3-bis(2-methoxyphenyl)propen-2-yl]-1H-imidazole,
1-benzyl-5-[3,3-bis(4-methoxyphenyl)propen-2-yl]-1H-imidazole,
1-benzyl-5-[3,3-bis(2,3-dimethylphenyl)propen-2-yl]-1H-imidazole,
1-benzyl-5-[3,3-bis(2-methylphenyl)propen-2-yl]-1H-imidazole,
1-benzyl-5-[3,3-bis(3-methylphenyl)propen-2-yl]-1H-imidazole,
4-[3,3-bis(2-methoxyphenyl)propyl]-1H-imidazole,
4-[3,3-bis(4-methoxyphenyl)propyl]-1H-imidazole,
1-benzyl-5-[3,3-bis(4-methylphenyl)propen-2-yl]-1H-imidazole,
or 1-benzyl-5-(3,3-diphenylpropen-2-yl)-1H-imidazole or a non-toxic pharmaceutically acceptable acid addition salt thereof.

11. A pharmaceutical composition comprising a substituted imidazole as claimed in any one of claims 1 to 10 and a pharmaceutically acceptable carrier.

12. An imidazole derivative as claimed in any one of claims 1 to 11 or a non-toxic acid addition salt for use in therapy as an aromatase inhibiting agent.

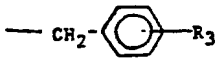
Claims for the following Contracting States: ES, GR

1. A process for the preparation of a substituted imidazole of the formula

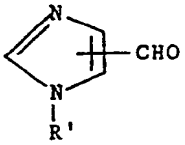


(I)

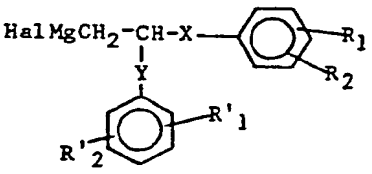
or a non-toxic pharmaceutically acceptable acid addition salt thereof wherein R_1, R_2, R'_1 and R'_2, which can be the same or different, are H, CH_3 C_2H_5, OCH_3, OH, CH_2OH, NH_2 or halogen; R' is H or



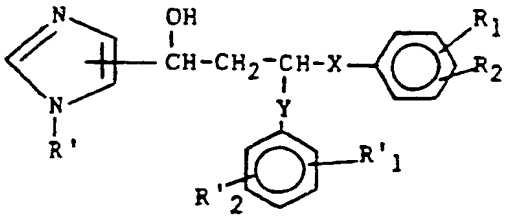
where R_3 is H, CH_3 or halogen; R_4 is H, R_5 is H and R_6 is H or OH or R_4 and R_6 together form a bond and X and Y which can be the same or different, are a bond, a straight C_{1-2}-alkyl or the corresponding alkenyl, which comprises reacting an 4(5)-imidazole aldehyde of the formula



with a Grignard reagent

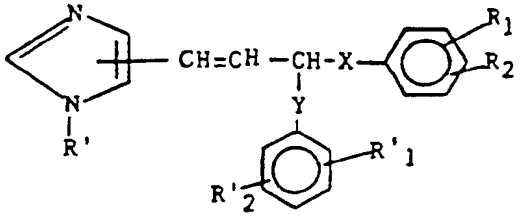


to give a compound of formula

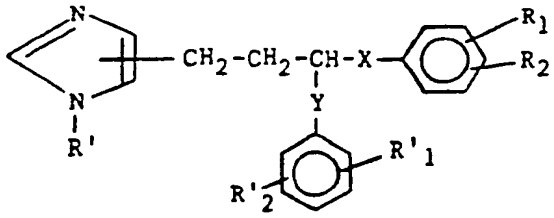


wherein R', R_1, R_2, R'_1, R'_2, X and Y are as defined before; dehydrating this product to give a compound

of formula

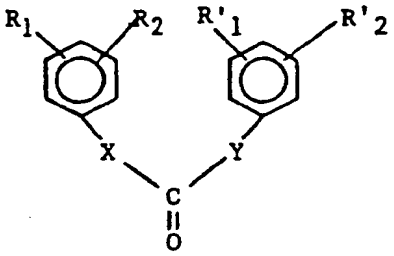


wherein R', R_1, R_2, R'_1, R'_2, X and Y are as defined before; and hydrogenating the product to give a compound of formula

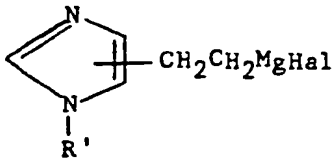


wherein R', R_1, R_2, R'_1, R'_2, X and Y are as defined before.

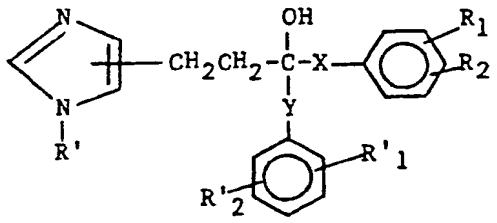
2. A process for the preparation of a compound of formula (I) as defined in claim 1 or a non-toxic pharmaceutically acceptable acid addition salt thereof wherein R_6 and R_4 are each H and R_5 is OH, which comprises reacting a ketone of the formula



with a Grignard reagent

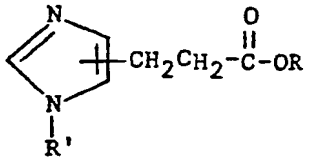


to give a compound of formula (I) which is

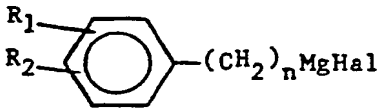


wherein R', R_1, R_2, R'_1, R'_2, X and Y are as defined before.

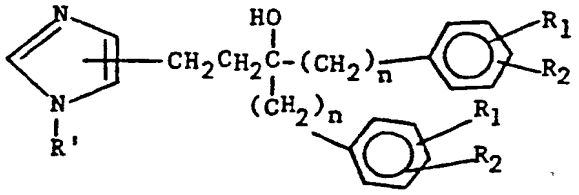
3. A process for the preparation of a compound of formula (I) as defined in claim 1 in which R_6 and R_4 are H, R_5 is OH and R_1 and R'_1 are identical and R_2 and R'_2 are identical or a pharmaceutically acceptable acid addition salt thereof,
which comprises reacting an 4(5)-imidazole propionic acid alkyl ester of the formula



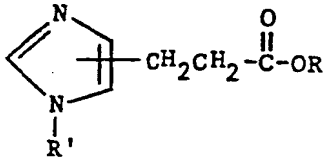
wherein R' is as defined in claim 1 and R is alkyl with a Grignard reagent of the formula



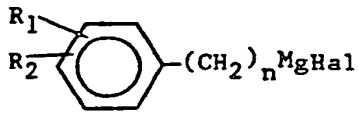
where R_1 and R_2 are as defined in claim 1 and n is 0 to 2 to give a compound of formula (I) which is



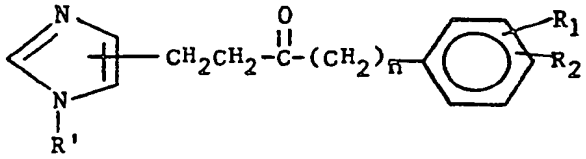
4. A process for the preparation of a compound of formula (I) as defined in claim 1 in which R_6 and R_4 are H and R_5 is OH or a non toxic pharmaceutically acceptable acid addition salt thereof
which comprises reacting an imidazole ester of the formula



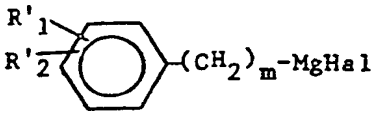
with a Grignard reagent



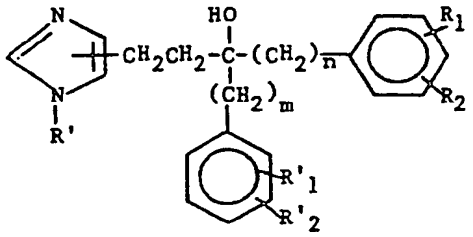
to give a compound of the formula



which further is reacted with another Grignard reagent of the formula

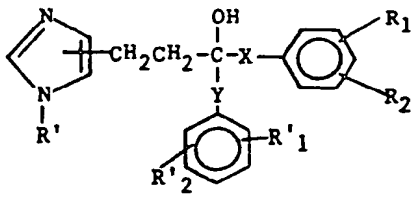


where R'_1 and R'_2 are as defined before and m is 0 to 2 to give a compound of formula (I) which is

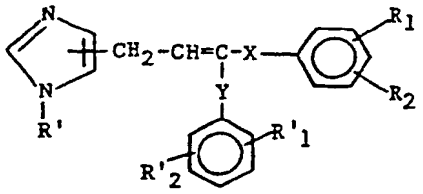


5. A process according to claim 3 or 4 wherein an 4(5)-imidazole propionic acid amide is used as starting material instead of the 4(5)-imidazole propionic acid ester.

6. A process for the preparation of a compound of formula (I) as defined in claim 1 in which R_6 is H and R_4 and R_5 together form a single bond or a non-toxic pharmaceutically acceptable acid addition salt thereof
which comprises dehydrating a compound of formula

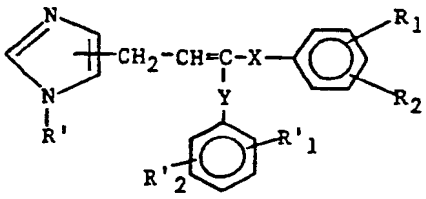


to give a compound of formula (I) which is

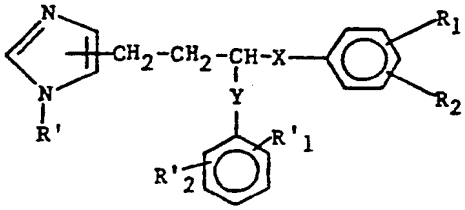


wherein R', R_1, R_2, R'_1, R'_2, X and Y are as defined before.

7. A process for the preparation of a compound of formula (I) as defined in claim 1 in which R_4, R_5, R_6 are each H or a non-toxic pharmaceutically acceptable acid addition salt thereof which comprises hydrogenating a compound of formula

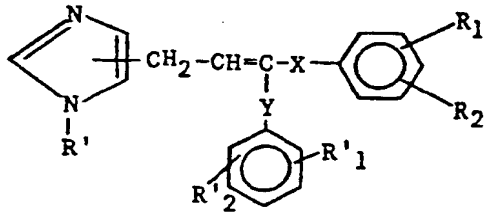


to give a compound of formula (I) which is

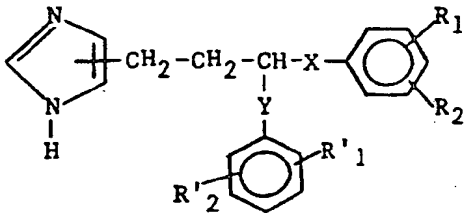


wherein R', R_1, R_2, R'_1, R'_2, X and Y are as defined before.

8. A process for the preparation of a compund of formula (I) as defined in claim 1 in which R_4, R_5, R_6 and R' are each H or a non-toxic pharmaceutically acceptable acid addition salt thereof which comprises hydrogenating a compound of formula

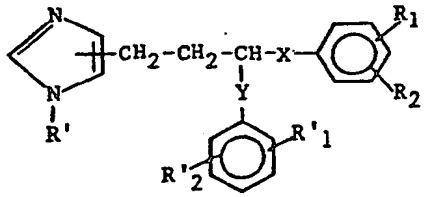


to give a compound of formula (I) which is

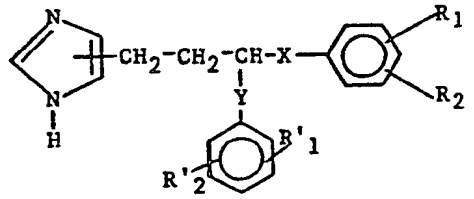


wherein R_1, R_2, R'_1, R'_2, X and Y are as defined before.

9. A process for the preparation of a compound of formula (I) as defined claim 1 in which R_4, R_5, R_6, and R' are each H or a non-toxic pharmaceutically acceptable acid addition salt thereof which comprises hydrogenating a compound of formula

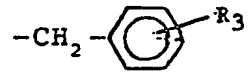


to give a compound of formula (I) which is

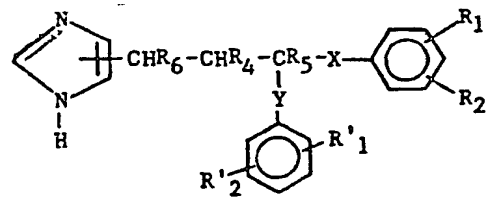


wherein R_1, R_2, R'_1, R'_2, X and Y are as defined before.

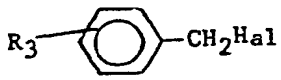
10. A process for the preparation of a compound of formula (I) as defined in claim 1 in which R' is



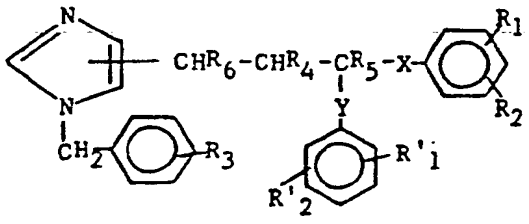
in which R_3 is as defined in claim 1 or a non-toxic pharmaceutically acceptable acid addition salt thereof which comprises reacting a compound of the formula



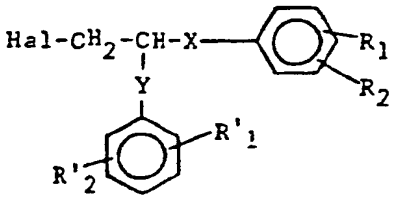
wherein R_1, R_2, R'_1, R'_2, R_4, R_5, R_6, X and Y are as d fined before with a strong base and further with a benzyl halide of the formula



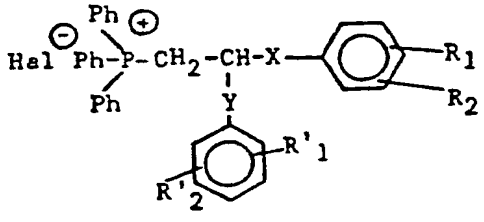
where R_3 is as defined before to give a compound of formula (I) which is



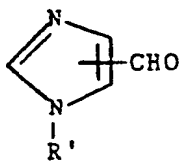
11. A process for the preparation of a compound of formula (I) as defined in claim 1 in which R_5 is H and R_4 and R_6 together form a single bond or a non-toxic pharmaceutically acceptable acid addition salt thereof
which comprises reacting a halogenated hydrocarbon of the formula



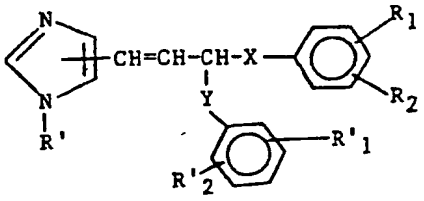
wherein R_1, R_2, R'_1, R'_2, X and Y are as defined before with triphenylphosphine to give a phosphonium salt of the formula



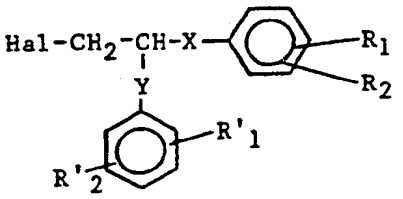
which is further reacted with a strong base and then with an 4(5)-imidazole aldehyde of the formula



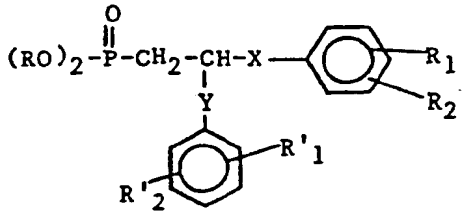
wh re R′ is as defined before to give a compound of formula (I) which is



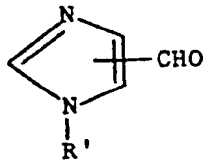
12. A process for the preparation of a compound of formula (I) as defined claim 1 in which R_5 is H and R_4 and R_6 together form a single bond or a non-toxic pharmaceutically acceptable acid addition salt thereof which comprises reacting a halogenated hydrocarbon of the formula



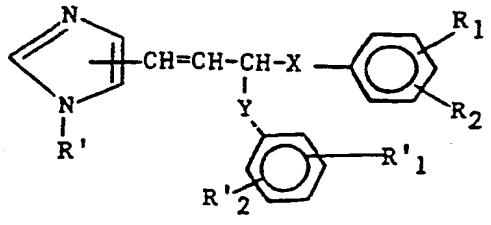
wherein R_1, R_2, R'_1, R'_2, X and Y are as defined before with a triester of phosphonic acid to give a compound of formula



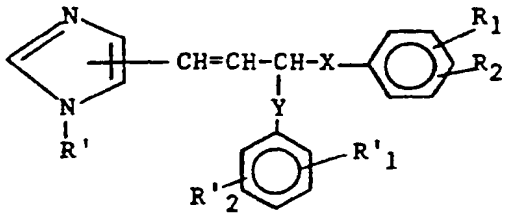
wherein R is alkyl, which further is reacted with a base and then with an 4(5)-imidazole aldehyde of the formula



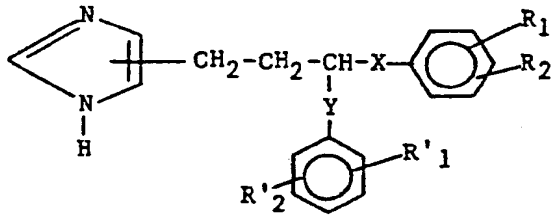
where R' is as defined before to give a compound of formula (I) which is



13. A process for the preparation of a compound of formula (I) as defined in claim 1 in which R_4, R_5, R_6, and R' are each H or a non-toxic pharmaceutically acceptable acid addition salt thereof which comprises hydrogenating a compound of formula



to give a compound of the formula (I) which is



wherein R_1, R_2, R'_1, R'_2, X and Y are as defined before.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 88 30 9413

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
A	EP-A-0 194 984 (CONTINENTAL PHARMA)		C 07 D 233/64 C 07 D 233/58 A 61 K 31/415
A	EP-A-0 165 779 (ELI LILLY)		
A	EP-A-0 072 615 (FARMOS GROUP)		
A	EP-A-0 064 820 (FARMOS-YHTYMA OY)		
A	EP-A-0 058 047 (FARMOS-YHTYMA OY)		
A	EP-A-0 034 474 (FARMOS-YHTYMA OY)		
A	EP-A-0 034 473 (FARMOS-YHTYMA OY)		

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

C 07 D 233/00
A 61 K 31/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	23-12-1988	DE BUYSER I.A.F.

CATEGORY OF CITED DOCUMENTS

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